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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
08/616,371	03/15/96	STAMLER J	DUK96-03PA

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EXAMINER	
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ART UNIT	**PAPER NUMBER**
1654	25

DATE MAILED: 08/26/99

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trad marks

file copy

Office Action Summary	Application No. 08/616,371	Applicant(s) Stamler, J.S.
	Examiner Bennett Celsa	Group Art Unit 1654

☒ Responsive to communication(s) filed on *Jun 10, 1999*.

☐ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *three* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *4, 5, and 9-29* is/are pending in the application.

Of the above, claim(s) _____ is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *4, 5, and 9-29* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☐ Notice of References Cited, PTO-892

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

Claims 4-5 and 9-29 are pending and under consideration.

Withdrawal of Finality: Reopening of Prosecution

Applicant's appellate brief, filed in paper no. 22 (dated 6/10/99) is acknowledged. However, prosecution is being reopened in order to give applicant an opportunity to clarify and ideally overcome the new and outstanding issues raised by this and the prior final office action.

Examiner Interview Summary Record

An attached copy of the Interview Summary Record of the personal interview conducted on 8/5/99 at the PTO has been entered. The Examiner wishes to thank Ms. Carol Egner, Mr. David Brook and Dr. Jonathan Stamler for the information and courtesies extended to this Examiner during this interview.

Abandonment of the 08/559,172 application

As formally requested by applicant's representative in the facsimile communication of July 9, 1999 the abandonment of the 08/559,172 application has been made of record.

Outstanding Objection(s) and/or Rejection(s)

The outstanding objection(s) and/or rejection(s) as presented in the final office action in paper no. 18 (dated 6/5/98) are still in force in their entirety. The Examiner will defer consideration of applicant's arguments directed to these rejections as presented in the appeal brief, since the response to the below rejection(s) may serve to further clarify the record and perhaps address some (or perhaps all) of the issues presented in the final office action.

New Objection(s) and/or Rejection(s)

1. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

2. Claims 9-15, 18-21, 26 and 27 are rejected under 35 U.S.C. 102(b) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Stamler et al, WO 93/09806 (5/93).

Stamler et al. discloses the therapeutic use of "low molecular weight" thiols, S-nitroso-protein and amino acid compounds (e.g. S-nitroso-hemoglobin or myoglobin) for regulating protein function, cellular metabolism including effecting vasodilation; increasing blood oxygen transport by hemoglobin and myoglobin; NO delivery; *in vitro* nitrosylation of molecules present in the body (e.g. see Abstract; pages 1-3 and claims). Stamler discloses a thionitrosylated hemoglobin composition (e.g. see page 58 and claims 13-16) comprising reacting hemoglobin in the presence of oxygen with a nitrosating agent (e.g. SNOAc) which composition anticipates that presently claimed. If equimolar amounts of nitrosating agent and Hb constitute "excess nitrosating agent" than the reference method anticipates the presently claimed method. Alternatively optimizing nitrosylating amounts to achieve "excess" nitrosation of hemoglobin to insure nitrosylation of hemoglobin would be obvious to the skilled artisan at the time of applicant's invention. The reference method of forming thionitrosylated oxygenated hemoglobin would either immediately envisage (e.g. anticipate) or alternatively render obvious the formation

of thionitrosylate deoxygenated hemoglobin under anaerobic conditions as presently claimed. The reference specifically discloses the use of nitrosylated proteins (e.g. S-nitroso hemoglobin) and low molecular weight nitrosating agents (e.g. see pages 1-2; page 24, lines 10-16) preparations thereof for the treatment of disorders by increasing oxygen capacity and transport; modulating CO and NO to tissues; scavenging radicals and vasodilation such as treating lung diseases (e.g. ARDS) and hypoxic disorders (E.g. see pages 19-25 and claims). The combination of nitrosating agents (e.g. thionitrosylated "Low" molecular weight and "high" molecular weight compounds; e.g. nitrosothiol, glutathione and hemoglobin) would be prima facie obvious to the skilled artisan at the time of applicant's invention in order obtain the increased pharmaceutical effects of the agents.

3. Claims 4-5 and 9-29 are rejected under 35 U.S.C. 103(a) as being unpatentable over Stamler et al. in view of Feola et al., U. S. Pat. No. 5,439,882 (8/95: filed 5/93 or earlier), Klatz et al., U.S. Pat. No. 5,395,314 (3/95: file 6/93 or earlier) and Hunter, U.S. Pat. No. 5,152,979 (10/92).

The discussion of the teaching of the Stamler et al. reference in the above rejection under 35 USC102/103 is hereby incorporated by reference in its entirety. To summarize, the Stamler et al .reference discloses the use of S-nitrosating agents (e.g. low molecular weight e.g. glutathione and hemoglobin derivatives) to treat disorders by achieving a variety of physiological effects including vasodilation; radical scavenging ; NO and oxygen delivery. The above reference does not explicitly disclose the use of nitrosating agent(s) to preserve living organs, treat malaria or

sickle cell anemia. Feola et al. disclose the use of "blood substitutes" to restore blood volume, transport oxygen and reduce vasoconstriction (e.g. vasodilate) by the use of hemoglobin alone or combined with glutathione as a blood substitute to treat blood disorders (e.g. sickle cell anemia) (e.g. see Abstract, examples and columns 1 and 7). Hunter discloses that malaria is a blood disorder which results in ischemia caused by compromised microvasculature (e.g. see abstract and col. 1). Klatz et al. disclose a brain resuscitation and organ preservation composition which comprises perfluorocarbons which act as "a blood substitute" which "transport(s) oxygen in a manner similar to hemoglobin" (e.g. see Abstract, col. 1, col. 4, lines 1-25). The Stamler et al. reference provides the skilled artisan with motivation to use nitrosating agents alone or combined to treat disorders of diseases to which vasodilation and oxygen/NO transport would prove to be therapeutic. It would have been obvious to the skilled artisan at the time of applicant's invention to utilize thionitrosating agents (e.g. hemoglobin, glutathione) as blood substitutes to treat blood disorders such as sickle cell anemia or malaria since the Feola reference discloses the use of hemoglobin and thiol containing blood substitutes to treat anoxic blood disorders (e.g. sickle cell anemia as disclosed by Feola and malaria as disclosed by Hunter) and Stamler provides a reasonable expectation that nitrosating agents will be successful to achieve the desired effects of blood substitutes. It would have been obvious to the skilled artisan at the time of applicant's invention to utilize nitrosating agents for organ preservation since the Katz reference provides motivation to utilize compositions such as perfluorocarbons for their ability to act as "blood substitutes" and hemoglobin oxygen transporters and Stamler teaches that nitrosating agents

would be successful to achieve the desired effects of blood substitutes and also act as effective hemoglobin oxygen transporters.

Discussion

Upon reconsideration, applicant's arguments and declaration of Dr. Stamler submitted in paper no. 13 (dated 2/23/98) in response to the above anticipation and/or obviousness rejections over the Stamler reference have been considered and deemed nonpersuasive for the following reasons.

The Examiner will address the Declaration evidence (and arguments) which parallel applicant's representative.

The first issue raised is the missing reagent issue. The declarant points out that Example 19 fails to indicate the identity of the nitrating agent which is reacted in equimolar concentrations with hemoglobin (e.g. 12.5 uM at pH 6.9). However, it is clear that the nitrating agent is SNOAc as recited in the rejection after reading page 58, lines 17-25 and this point is easily confirmed by applicant's own previous application e.g. in Example 1 of 08/559,172, the reaction of SNOAc and hemoglobin in equimolar amounts (and presumably under the same conditions), **achieves the same spectrophotometric evidence** of S-nitrosothiol bond formation. E.g. compare Figures 28 and 29 of WO 93/09806 to Figures 1 and 2 of the 08/559,172. Accordingly, the WO 93/09806 reference undisputably discloses the reaction of a low molecular weight nitrosothiol (e.g. SNOAC) with hemoglobin.

Whether applicant actually performed the experiment or the acidified nitrate experiment in his laboratory is irrelevant to the disclosure by the reference of the reaction between SNOAc and hemoglobin. The Declarant's catching of a mistake with regard to maximum absorbance (e.g. 450nm) when the graph clearly shows a maximum absorbance of 540nm is acknowledged by the Examiner. However, the declarant's point that one can not measure or distinguish SNO-hemoglobin from hemoglobin at a particular absorbance or that there is not any real confirmation of the presence of SNO-hemoglobin **is not the same as proving the absence of SNO-hemoglobin**. Applicant' s own specification demonstrates that reacting a low molecular weight S-nitrosothiol such as SNOAc in equimolar amounts with hemoglobin (e.g deoxy or oxy) would be expected to generate SNO-hemoglobin (e.g. see present specification at pages 46-48 and Figures 1a-1d). It is also noted that use of extrinsic evidence by the Examiner to demonstrate inherency is permitted (e.g. see MPEP 2131.01(d)), *including the use of applicant's own specification* (e.g. examples). See *Ex parte Novitski*, 26 USPQ2d 1389 (B.P.A.I, 1993).

The Declarant's attempt to reproduce the Reference Example 19 method was not found persuasive since it is unclear as to whether applicant is showing the absence of SNO-hemoglobin or the inability of the utilized assay to detect the presence of SNO-hemoglobin. It is also noted that applicant's claimed composition "comprises" SNO-hemoglobin and therefore encompasses mixtures of SNO-hemoglobin with other hemoglobin species. The Examiner also is unable to reconcile the Declarants' experimental results with those experimental results and statements in the specification which assert that reacting low molecular weight nitrosothiols with oxygenated

hemoglobin in 1:1 ratio would form some amount of SNO-hemoglobin (again see specification pages 46-48 and Fig. 1a-1d); and additionally Example 1 and Figures 1 and 2 in application Serial No. 08/559,172 which confirms the presence of a "composition which comprises SNO-hemoglobin" within the scope of the presently claimed invention. The Declarant's problem regarding pH and concentration is not seen by the Examiner as problematic where one would be motivated to increase the amounts of nitrosating agent as pointed out in the rejection and optimize other reaction parameters (e.g. pH) as a matter of course. The Declarant's further statement regarding the veracity of reference statements regarding "reaction at the heme" are again not commensurate in scope to the claims which broadly include "compositions comprising S-nitrosohemoglobins" and additionally fail to address the optimization of reaction parameters (e.g. increasing nitrating agent relative to hemoglobin) concentration which is obvious to one of ordinary skill. The Declarant's assertion that pH 6.9 cannot be used to form SNO-hemoglobin is rebutted by page 16 of 08/559,172 which appears to show the formation of S-nitrosyl hemoglobin at this pH in addition to higher pH optimums. In light of the reference disclosure, applicant's own disclosure in the present application and the disclosure provided in 08/559,172 applicant's proffered declaration and attorney argument can not be considered persuasive. It is also noted that the Declarant's and attorneys arguments are not commensurate in scope to the claimed invention; nor do they adequately address the optimization of reaction conditions specifically pointed out in the obviousness rejections above.

With regard to the second obviousness rejection above (e.g. Stamler in view of Feola and Klatz) applicant's arguments directed to the Stamler reference have already been addressed above. Applicant's argument of the Feola and Klatz references separately, is not persuasive insofar that the above rejection is clearly a combination of Stamler taken in view of Feola and Klatz. Applicant further argues that Stamler does not specifically describe any nitrosated hemoglobin or any effects of nitrosated hemoglobin. However, as pointed out in the rejection, the Stamler reference clearly *discloses* the use of nitrosylated proteins generically and nitrosylated hemoglobin specifically to produce the desired effects. Applicant's argument regarding the inability of the Stamler reference to enable the making of specifically S-nitrosylated hemoglobin has already been addressed above. The Examiner again asserts that applicant's claims are not restricted only to the use of an S-nitrosylated hemoglobin compound but are generically broader to include a mixture of S-nitrosylated hemoglobin and other hemoglobin derivatives to which the Stamler reference is enabled by its disclosure and its examples taken separately or in view of obvious modifications thereof (e.g. optimization of reactions and experimental conditions).

Accordingly, the above rejections are hereby maintained.

General information regarding further correspondence

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Examiner Celsa whose telephone number is (703) 305-7556.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Woodward, can be reached at (703)308-4028.

Any inquiry of a general nature, or relating to the status of this application, should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Bennett Celsa
August 25, 1999